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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,133	BILBE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2008 and 22 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-44* is/are pending in the application.

4a) Of the above claim(s) *27-39,43 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 11/7/2005, in which claims 1-26 were canceled, and claims 27-44 were added. Claims 27-44 are pending.

Election/Restrictions

Applicant's election without traverse of Group IV (claims 40-42) in the reply filed on 3/10/2008 is acknowledged. Applicant's election without traverse of the combination of genes of NMDAR2 (AF001423), Glu-binding subunit (Grina) (S61973); Densin-180 (U66707); Begain (AF064868); CAMKII gamma (J04063); CAMKII inhibitor alpha (AA858621); Synapsin II (AI145494), SNAP-25A (AB003991); SNAP-25B (AB003922); VAMP2 (AI101103); and Adenylyl cyclase 2 (AI145367) in the reply filed on 7/22/2008 is acknowledged.

Claims 27-39, 43 and 44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/10/2008.

An examination on the merits of claims 40-42 follows.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/395,088, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Application No. 60/395,088 fails to disclose the genes of instant Table 7. Thus the application fails to provide adequate support or enablement for the elected method, which is drawn to the NMDA R2 (AF001423), SNAP-25A (AB003991), and SNAP-25B (AB003992) genes disclosed only in Table 7 (and not Table 1) of the present specification.

Claims 40-42 have been assigned an effective filing date of 5/22/2003 (the filing date of 60/472,489).

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The residence and post office address of Anu Kinnunen have been altered without being initialed and dated.

Specification

The abstract of the disclosure is objected to because it contains legal phraseology such as "said disorders" (line 2). Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See pages 42 and 43.

The use of the trademarks RNEASY (paragraph bridging pages 39-40), TAQMAN (pages 46 and 48-50), and OMNISCRIPT (page 48) has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Claim 41 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 41 is drawn to genes selected from the group consisting of Tables 1, 2 and 7, whereas independent claim 40 is drawn to genes selected from the group consisting of Tables 1 and 7 or selected from the group consisting of Table 2. Accordingly, claim 41 is broader in scope in that it broadens the scope of the Markush-type groups from which the genes are selected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to a method for monitoring the efficacy of a treatment of a subject having schizophrenia, bipolar disorder and/or ADHD or at risk of developing schizophrenia, bipolar disorder and/or ADHD with an agent. The elected species of invention is drawn to the steps of a) obtaining a pre-administration sample in the frontal lobe from the subject prior to administration of the agent; b) detecting, in the pre-administration sample, a level of expression of the following genes: NMDA R2 (AF001423); Glu-binding subunit (Grina) (S61973), Densin-180 (U66707); Begain (AF064868); CAMKII gamma (J04063); CAMKII inhibitor alpha (AA858621); Synapsin II (AI145494); SNAP-25A

(AB003991); SNAP-25B (AB003992); VAMP2 (AI101103); and Adenylyl cyclase 2 (AI145367); c) obtaining one or more post-administration samples from the subject; d) detecting a level of expression of said genes in the post-administration sample or samples; e) comparing the level of expression of said genes in the pre-administration sample with the level of expression of the at least one gene in the post-administration sample; and f) adjusting the administration of the agent accordingly. The nature of the invention is complex in that the comparison step must provide a predictable indicator of the efficacy of treatment.

As written, the claims refer to tables that define the genes by GenBank accession number. The specification specifically notes that the genes of the invention are available from public databases (NCBI) using the accession numbers shown in Table 1, 2, 5, 6 and 7 (e.g., sentence bridging pages 11-12). Further, Table 1 indicates that the "Accession number can be used to identify the unique identity of each gene at NCBI – UniGene at http://www.ncbi.nlm.nih.gov/UniGene/" (page 42). "Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. In the instant case, the claims are, in effect, incorporating the sequence of the GenBank accession numbers by reference to the entries in the electronic database. "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." See MPEP 608.01(p) [R-3]. Accordingly, the reference to the GenBank accession

numbers does not provide the features that are critical or essential to the practice of the claimed invention.

Breadth of the claims: The claims are broad in that they are drawn to a method of monitoring the efficacy of treatment with any drug for schizophrenia, bipolar disorder, and/or ADHD, or risk thereof. The claims are broadly drawn to monitoring the efficacy of treatment in any subject of any species (e.g., human, rat, mouse, etc.); however, the sequences of Tables 1 and 7 (listed above) are GenBank accession numbers for rat sequences. Further, the comparison made in the claims is broad in that the sample type(s) of the post-administration samples is not specified by the claim. Thus, the claims encompass embodiments where gene expression in the frontal lobe is compared to gene expression from blood, muscle, liver, etc. Moreover, the claims encompass any changes in expression that may be observed in the comparison: no change, increases of some or all of the genes, or decreases in some or all of the genes. The step of adjusting the administration of the agent must be done "accordingly," but the claims do not tie specific changes in gene expression to a specific adjustment for a particular drug for the treatment of a particular disease. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification teaches that the prefrontal cortex, which is part of the frontal pole, is a target for glucocorticoids involved in the stress response, and it regulates the negative feedback of the HPA axis (e.g., paragraph bridging pages 7-8). To model schizophrenia, the inventors have incorporated stress in a form of repeated variable prenatal stress to pregnant Sprague-Dawly rats in a randomized manner during the last week of pregnancy (e.g., page 12, paragraph 1; Example 1). At postnatal

day 56 (P56), the rats born from stressed mothers were put through an acute stress procedure involving an acclimation period of 5-7 days in the laboratory environment to re-establish homeostasis, and subsequent subjection of the prenatally stressed offspring, and the non-stressed to a cylindrical plastic restrainer for 30 min. At the end of the acute restraint session, the animals were either sacrificed by decapitation or returned to their cages to be sacrificed at 120 min or 24 hours after removal from the restraint device. A baseline group was also collected to establish baseline gene expression levels without exposure to acute stress (e.g., page 38, paragraph 2). Behavioral assessment of the rats indicated that prenatal stress exposure induced a heightened locomoter response to both amphetamine and phencyclidine, caused disrupted sensorimotor gating assayed by both PPI and N40, and resulted in deficits in glucocorticoid feedback (e.g., paragraph bridging pages 38-39). To identify potential diagnostic markers and therapeutic targets, RNA isolated from the frontal pole was hybridized to a rat genome RG-U34A microarray (e.g., Example 2). The results were carefully analyzed by multiple normalization procedures and statistical tests to arrive at the genes consistently differentially expressed between prenatally stressed rats compared to non-stressed rats. These genes are presented in Table 1. Table 1 includes the following elected genes: Glu-binding subunit (Grina) (S61973), Densin-180 (U66707); Begain (AF064868); CAMKII gamma (J04063); CAMKII inhibitor alpha (AA858621); Synapsin II (AI145494); VAMP2 (AI101103); and Adenylyl cyclase 2 (AI145367). The following genes were upregulated in stressed rats relative to non-stressed rats: Densin-180 (U66707); Begain (AF064868); and Synapsin II (AI145494). The following genes were downregulated in stressed rats relative to non-stressed rats: Glu-binding subunit (Grina) (S61973); CAMKII gamma (J04063); CAMKII inhibitor alpha (AA858621); and VAMP2

(AI101103). Further gene expression studies were performed to compare the response at different time points and differentially expressed genes are presented in Table 7. The following genes were increased in the prenatally stressed rats at baseline: NMDA R2 (AF001423); Densin-180 (U66707) (also at 30 min and 24 hours); and Begain (AF064868). Synapsin II (AI145494) expression was increased after 24 hours. SNAP-25A (AB003991) and SNAP-25B (AB003992) had decreased expression in prenatally stressed rats at baseline. VAMP2 (AI101103) expression was decreased in prenatally stressed rats after 24 hours.

The specification does not teach how drugs capable of treating schizophrenia, bipolar disorder and/or ADHD or drugs capable of treating subjects at risk of developing schizophrenia, bipolar disorder and/or ADHD alter the expression patterns of the claimed genes. Gene expression changes are not measured for efficacious responses to the drugs. The specification does not teach the gene expression changes in the frontal lobe after administration of the drugs when the drug is effective and when the drug is not effective such that one could use the gene expression changes as an indicator of efficacious treatment. The specification does not contain a working example of the claimed method.

Predictability and state of the art: The art teaches that gene expression analysis is commonly used for three different purposes: (1) as a screening tool to identify individual genes of interest that might contribute to an important biological function, (2) to obtain insight into an important biological function, and (3) as a classification tool to sort cases into clinically important categories (Pusztai and Hess, Annals of Oncology, Vol. 15, pages 1731-1737, 2004; e.g., paragraph bridging pages 1732-1733). In the instant case, the specification uses gene expression analysis to identify genes of interest and obtain insight into an important biological

function in a rat model of schizophrenia. However, the claims are drawn to using gene expression analysis to classify a subject as responding or not responding to a treatment such that the administration of the treatment can be adjusted and be made effective. The gene expression levels of the claimed genes must be indicative of the level of effectiveness of the treatment administered to the subject (e.g., human, rat, etc.). Pusztai and Hess teach that validation of gene expression important to biological function may be validated by using different methods, such as RT-PCR, whereas the most appropriate validation for using gene expression analysis as a classification tool is testing the predictor on independent sets of cases (e.g., page 1733, left column, 1st full paragraph). In the instant case the specification provides a prophetic example for validation by RT-PCR (e.g., Example 3) and provides a prophetic example for validation of the differentially expressed genes in the animal model by known drugs to schizophrenia, ADHD, and bipolar disorder (e.g., Example 4). The specification does not teach the changes in gene expression specific to any of these drugs in the rat model or a human subject, for example. The specification states, "Since there is no way of determining if an individual is susceptible to schizophrenia, it is currently unknown in these antipsychotic compounds are useful in the prophylactic treatment of schizophrenia." See paragraph bridging pages 6-7. Thus, it would be unpredictable to determine the efficacy of treatment for a subject at risk of developing schizophrenia, bipolar disorder and/or ADHD. Moreover, the specification does not validate the changes in gene expression observed for the rat in any other subject (e.g., human), and it would be unpredictable to use rat sequences to detect expression in the full breadth of subjects claimed.

Further, Shalon et al (US 2001/0051344 A1, Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the

expression of a gene between any two individuals may or may not be significant (e.g., paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (e.g., paragraph [0156]). Pusztai and Hess teach that larger samples sizes may be needed to validate classification tests, and the number of samples will vary depending upon the acceptable error rates, level of inter-patient variability, the size of the difference in mean expression values, and the prevalence of the phenotype among the group being tested (e.g., page 1734, paragraph bridging columns; Table 1).

The prior art reveals that differences in gene expression observed between two groups are do not necessarily provide markers that can be used to reliably classify a subject. Golub et al (Science, Bol. 286, pages 531-537, October 1999) teach the use of a two-step procedure to test the validity of gene expression levels as predictors: step 1 involves cross-validation of the predictors on the initial data set, where one withholds a samples, builds a predictor based only on the remaining samples and predicts the class of the withheld sample; step 2 involves the repetition of assessing the clinical accuracy of the predictor set on an independent set of samples (e.g., page 532, right column). Although Golub et al could detect gene expression differences between chemotherapy responders and non-responders, those differences could not be use to predictably classify individuals (e.g., page 533, paragraph bridging left and middle columns). Accordingly, the art demonstrates the unpredictable nature of extrapolating gene expression differences to a method of class prediction for efficacy of treatment.

The use of gene expression patterns to determine efficacy of treatment would have been an unpredictable venture when the gene expression changes are not empirically determined for a specific drug. For example, Beaudry et al (Journal of Neurochemistry, Vol. 75, pages 1694-1702, 2000) teach that contrasting patterns of NGFI-B mRNA expression were observed with a typical or an atypical antipsychotic drug administration after both acute and chronic treatments (e.g., page 1695, right column, 1st full paragraph). In animals chronically treated with clozapine, all brain regions analyzed showed significant decrease of NGFI-B mRNA levels compared with the vehicle-treated group (e.g., paragraph bridging pages 1697-1698; Figure 5). In contrast, NFGI-B mRNA levels were strongly elevated in the dorsolateral striatum of animals treated with haloperidol (e.g., paragraph bridging pages 1697-1698; Figures 4 and 5). Further, Chong et al (Journal of Neurochemistry, Vol. 82, pages 1533-1539, 2002) employed cDNA expression array technology to explore the chronic effects of haloperidol on gene expression in the rat striatum (e.g., page 1534, left column). Chong et al teach that chronic haloperidol treatment increased synapsin II expression 1.56-fold in the striatum relative to control animals (e.g., Table 1); however, Chong et al teach that the effects of haloperidol on synapsin II expression may vary among the different regions of the brain (e.g., page 1538, left column, 2nd paragraph). The effect of the drug on gene expression cannot be predicted. Studies must be performed to determine the gene expression levels (Chong et al. page 1538, left column, 2nd paragraph). Furthermore, variable expression between different brain regions and tissues makes it unpredictable to use any sample type for the post-administration sample of the claims.

Even if the claimed genes were reliable gene expression markers for efficacious drug treatment in rat, it would be unpredictable to extrapolate these results to human. For example,

the specification teaches that synapsin II expression is increased in the frontal lobe of stressed rats as compared to non-stressed rats (e.g., Table 1). However, Imai et al (Neuroscience Letters, Vol. 305, pages 185-188, June 2001) teach that synapsin II mRNA levels in the prefrontal cortex of human schizophrenic patients is not significantly different than the level of expression in the prefrontal cortex of human non-schizophrenic subjects (e.g., paragraph bridging pages 185-186). Accordingly, one of skill in the art would have recognized that it would have been unpredictable to extrapolate the results of gene expression studies in the rat to gene expression levels in other animals such as humans.

Amount of experimentation necessary: Given the lack of guidance in the specification and prior art with regard to changes in gene expression of the claimed genes upon administration of drugs used to treat schizophrenia, bipolar disorder and/or ADHD, or risk thereof, one would be required to carry out a large amount of experimentation to determine how to use changes in gene expression of the claimed genes to determine the efficacy of treatment. One would be required to determine the changes in gene expression in the rat frontal lobe upon administration of a specific drug, provided at a dose known to provide efficacious treatment. Next, one would be required to test whether the changes in gene expression are a reliable indicator of treatment efficacy. This would need to be repeated for the large number of drugs encompassed by the claims. Furthermore, one would have to perform additional experimentation to determine how to use the rat claimed rat gene sequences to identify changes in gene expression in other organisms encompassed by the claims.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an

undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 40-42 are not considered to be enabled by the instant specification.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
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